#6
5/20/04
A.W.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Garner et al.	Group Art Unit: 2177
Serial No. 09/865,090	Examiner: Wong, L.
Filed: May 24, 2001	Attorney Docket No. UTSD:0668
For: *Program for Microarray Design and Analysis*	

DECLARATION UNDER 37CFR1.132

I, Harold R. Garner, declare and state as follows:

1. I currently serve as the P.O'B Montgomery Distinguished Professor of Biochemistry and Internal Medicine at the University of Texas Southwestern Medical Center. I am a founder of the Center for Biomedical Inventions at the University, and have authored hundreds of research papers, and am a recognized expert in the field of applied computational biology. I am an inventor of the subject application.

2. Wolffe et al. (US 2002/0081603 A1) describe methods for characterizing DNA sequences, and disclose that known computer-based methods, such as alignment tools, can be used to compare identified regions with known sequences. Wolffe protocol is neither applicable nor germane to the field of our invention (and conversely, our invention is neither applicable nor particularly germane to his). Wolffe identifies accessible genomic sequences, and characterizes them as regulatory sequences using known alignment algorithms. We disclose and claim a novel protocol for generating targeted collections (e.g. sequence arrays) of sequences from a dataset of sequence identifiers corresponding to natural complex biopolymer sequences (e.g. syngeneic sequences) and linked to corresponding annotations.

Wolffe does not provide for reducing redundancy of initial search results by mapping to a database correlating sequence identifiers with syngeneic biopolymers to generate a second dataset subset (our claim1, step (b)). Wolffe is characterizing sequences – Wolffe is not in the business of generating syngeneic datasets. Hence, Wolffe necessarily has no provision for further processing a resultant second dataset subset, as required by our claim 1, steps (c) - (d). Note that analogous required steps for reducing redundancy of the initial search results by mapping to a database correlating sequence identifiers with syngeneic biopolymers are present in all of our claims (e.g. step (b) of claim 13, and step (a) of claims 14, 17, 18 and 20).

How is it possible to transform a method of characterizing regulatory sequences using alignment tools into the claimed method of generating targeted collections (e.g. sequence arrays) of sequences from a dataset of sequence identifiers corresponding to natural complex biopolymer sequences (e.g. syngeneic sequences) and linked to corresponding annotations?

Hennig et al. (2000, Annual Conference on Research in Computational Molecular Biology *p. 165-173; INVITED PRESENTATION: A data-analysis pipeline for larger-scale gene expression analysis)* describe a method for characterizing cDNA clone libraries based on oligo

fingerprints (OFPs). In this method, EST clones are amplified by PCR, immobilized on filter membranes, and hybridized in separate, parallel incubations to different, known-sequence radiolabeled oligo probes, providing corresponding different hybridization signals for each clone – an oligo fingerprint. Hennig, p.166, first full para.

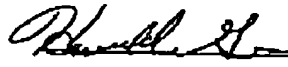
Oligo fingerprints can be used to identify a subset of low redundant EST clones for genome sequencing efforts: specialized algorithms can be used to cluster clones according to oligo fingerprints and then representative clones from each cluster can be selected to generate a less redundant EST set, which will (hopefully) be representative of the original EST libraries in terms of containing representatives of all the originally represented genes. In theory, such a subset reduces the number of clones which need to be sequenced (p.166, second full para), though in practice, the method is quite imperfect (p.170, first full para.).

How does the practitioner of Wolffe find applicable relevance in Hennig, and to what end? Wolffe is characterizing novel regulatory sequences by using alignment tools to compare them with known sequences. Hennig is characterizing large EST libraries based on oligo fingerprinting, so as to reduce the number of clones that need to be sequenced. The Action proposes that Hennig's teachings would have allowed Wolffe to clean, remove duplicates, and perform quality checks to the raw sequence in preparation for the sequence comparison analysis. Action, p.4, lines 6-8. Clean what? Remove duplicates of what? Perform quality checks on what raw sequence? The proposed combination does not survive scrutiny.

Wolffe compares his identified sequences with reference sequences such as in Genbank to generate "hits", such as by using the BLAST algorithm. Of course, to the extent a Wolffe practitioner is generating original sequence, she may well seek to improve the relevance of her sequencing by sequencing multiple sample copies, and using algorithms to identify and discount artifactual sequences. This is not really analogous to what Hennig is doing: spotting duplicate probes to insure accuracy of each probe-EST correlation. But it could be argued to be general motivation to repeat data points and improve accuracy. However, as much as coopting Hennig's data cleaning, removing duplicates, and performing quality checks may improve accuracy, it has not driven Wolffe's practitioner into a different line of work.

My coinventors and I appreciate that the claimed subject matter is arcane and not easy to examine; however, we believe that the presently cited art does not provide a remotely colorable suggestion of the subject claims. We believe that our Specification provides a detailed description, analysis and distinction of prior work that those skilled in the art would find most relevant to our invention. We have laid out the features of such prior work, including the computational tools known as DRAGON, POMPOUS, Rep-X, etc., identified their deficiencies, and explained how our invention improves upon them.

3. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application and any patent issuing therefrom.

Date: 5/10/04  Prof. Harold R. Garner